REMARKS

This Reply is responsive to the Office Action dated December 19, 2001. Entry of the amendments and remarks submitted herein and reconsideration pursuant to 37 CFR §1.112 is respectfully requested.

At the outset, Applicants respectfully request consideration of the Doolittle reference, which the Examiner indicated had not been considered on the prior PTO-1449 form, apparently because the year of publication was not clear. Another copy of the Doolittle reference is attached hereto, where it can be seen that the year of publication was 1979. A second PTO 1449 form has also been included for the Examiner's initials.

The specification was amended above to include reference to SEQ ID Nos in the Figure legends as requested in the Office Action, and to correct inadvertent spelling errors. A new sequence listing accompanies this amendment, which includes SEQ ID Nos newly assigned to various sequences in Figures 3 and 4 which were not previously included. No new matter was added.

Claim 14 was canceled and claims 15, 16 and 32 were amended so as not to depend from a non-elected claim. Claim 32 was also amended to specify that the claimed kit distinguishes differentiated and dedifferentiated chondrocytes as discussed, for example, at page 21 of the specification, lines 12-14, and at page 2, lines 1-5. Claim 17 was amended to include the definition for stringent hybridization conditions provided at page 16, lines 20-21. No new matter was added.

In addition, new claims 33-38 were added that define the isolated nucleic acids by virtue of the amplification primers used to isolate them. Support for these claims may be

found at the very least at page 23, lines 6-19, at page 28, line 10, and at page 30, lines 1-7. No new matter was added.

Turning now to the Office Action, the Examiner has acknowledged applicant's claim for foreign priority based on PCT/JP98/05348 and JP342060/1997. However, priority has been denied because certified copies of the applications have allegedly not been submitted. Applicants respectfully note that this application is a 371 national stage application of PCT/JP98/05348, therefore, no certified copy is required of the PCT application. Furthermore, according to Form PCT/IB/304, a copy of which is attached hereto, a copy of the priority document JP97/342060 was received by the International Bureau, and therefore should have been received at the U.S. Patent & Trademark Office along with the other national stage papers. For the Examiner's convenience, applicants have included an English translation of the priority document with this submission. In view of the above, applicants respectfully request verification of the priority claim, which would entitle applicants to a foreign priority date of 10-27-97, which is the filing date of JP97/342060.

The examiner objected to the specification for failing to include SEQ ID Nos in the figure legends. The specification was amended above to correct this deficiency, and a new sequence listing is attached hereto that incorporates the newly added SEQ ID Nos. Therefore, this objection should now be withdrawn.

Claim 32 was objected to because it recited non-elected inventions. Claim 32 was amended above to delete non-elected subject matter, therefore, this objection may be withdrawn.

Claims 14-17 and 32 were rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness. Specifically, claims 14-16 and 32 were alleged to be indefinite because they depend on non-elected claims. Claim 14 was canceled above and claims 15, 16 and 32 were amended so as not to depend on any non-elected claim. Therefore, the rejection under §112, second paragraph as to these claims may now be withdrawn.

Claim 17 was alleged to be indefinite because it is drawn to stringent hybridization conditions, and such hybridization conditions are not defined in the claim. According to the rejection, the specification fails to provide a standard for ascertaining the requisite degree of stringent conditions and therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants respectfully traverse.

It is the specification which should provide the definition for the terms used in the claims, and in contrast to what is alleged in the Office Action, the specification provides a definition for stringent hybridization conditions on page 16, lines 11-21. As described therein, stringent conditions may be described in a concrete manner as including a wash temperature ranging from the Tm of a hybrid of completely matching nucleic acids to a temperature 20°C lower than the Tm, or as conditions at which DNA's having homology of 80% or more are hybridized, but at which nucleic acids having lower homology are not hybridized. Therefore, one of skill in the art would know what "stringent hybridization" means in claim 17 by reading the specification. Nevertheless, the definition recited at page 16 has been incorporated into claim 17 to resolve any ambiguity. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 14-17 and 32 were rejected under 35 U.S.C. §101 for being directed to non-statutory subject matter. Specifically, the claimed DNAs and gene were alleged to have the same utility as the DNA or gene found naturally. Claims 15-17 have been amended to indicate that the claims DNA's and gene are isolated. Therefore, this rejection under §101 may now be withdrawn.

Claims 14-17, 25-28 and 32 were also rejected under 35 U.S.C. §101 as allegedly failing to be supported by either a specific asserted utility or a well established utility. The following bases for the rejection were reported:

(1) The specification allegedly fails to teach what CDEP is and what it does, and no utility is provided for any of the fragments described.

(2) The utilities that are asserted, such as production of and screening of antibodies, allegedly apply to many unrelated polypeptides and are therefore not "specific" to CDEP.

(3) Additional asserted utilities such as therapy of osteoarthritis and rheumatoid arthritis, and screening regulators of cell differentiation are based on homologies to ezrin, Dbl and pleckstrin. However, the Examiner questions whether CDEP would have the same functions as these homologous proteins because homology is not 100%, and sequence dissimilarities upon protein structure and function allegedly cannot be predicted. This aspect of the rejection is supported by several references which purportedly show the sensitivity of proteins to single amino acid substitutions, and which stress the pitfalls of comparative sequence analysis.

(4) The examiner also notes that the claimed nucleic acid is not specific for differentiated chondrocytes because it is detected in other tissues, and that the disclosed probes are not specific for SEQ ID NO: 1 because two bands were detected in northern blotting analyses using a CDEP-specific probe.

(5) Finally, according to the Examiner's reasoning, even if CDEP expression was specific for differentiated chondrocytes, this still would not satisfy the new utility standards because other nucleic acids are specific for differentiated chondrocytes. Therefore, the asserted utility would still not be "specific" to CDEP.

These bases for the rejection will be addressed sequentially for the examiner's convenience.

The first point raised in the rejection is that the specification allegedly fails to teach what CDEP is and what it does, and no utility is provided for any of the fragments described. Applicants respectfully submit that the specification provides a detailed discussion as to why CDEP is predicted to be a member of the Rho-GEF family, thereby suggesting that CDEP plays an important role in controlling the adhesion, diffusion, migration, proliferation, and differentiation of cells, including chondrocytes. See page 12, lines 1-19; see also pages 33-35. As such, the nucleic acids and fragments thereof disclosed in the specification may be used at the very least to distinguish differentiated cells from non-differentiated or dedifferentiated cells, and particularly differentiated chondrocytes. Such utility is further supported by the fact that CDEP was identified using subtractive hybridization to identify RNAs expressed in differentiated chondrocytes but not dedifferentiated chondrocytes. See page 2, lines 1-5, and page 26, lines 1-19.

Further support is provided by experiments which analyzed the location of the CDEP protein in cartilage tissue *in vivo*, and which looked at the timing of the induction of CDEP mRNA expression in an *in vitro* chondrocyte culture system. See pages 31-32. In particular, expression of CDEP is elevated in the presence of parathyroid hormone (PTH) and cAMP, which are known to modulate the differentiation of chondrocytes. See page 32, lines 6-8.

As a gene involved in chondrocyte differentiation, CDEP and fragments thereof may be used to induce or maintain the differentiation of chondrocytes. See page 34, lines 23-24. Such a use may make it possible to control the differentiated state of chondrocytes playing deviating roles in arthropathies such as osteoarthritis. See the sentence bridging pages 34-35. In addition, since other Rho-GEF family members are known to become oncogenes as a result of certain N-terminal deletions, CDEP may serve as a target for the design of new cancer therapeutics if it shows the same oncogenic potential as other Rho-GEF family members. See page 35, lines 3-10.

The fact that CDEP has Rho-GEF activity, as predicted in the specification, has since been confirmed and published as shown in the article by Koyano et al. attached hereto ("Chondrocyte-derived ezrin-like domain containing protein (CDEP), a rho guanine nucleotide exchange factor, is inducible in chondrocytes by parathyroid hormone and cyclic AMP and has transforming activity," Osteoarthritis & Cartilage (2001) 9, Suppl. A, S64-68). As reported in this article, dissociation of ^{3}H-GDP from ^{3}H-GDP-RhoA was induced dose-dependently by Sf9 cell lysates containing a recombinant GST-CDEP peptide containing the DH and PH domains, but not by control lysates (see page

S65, col. 1). In addition, Koyano et al. (2001) also reports that transfection of an N-terminal truncated CDEP cDNA induced focus formation of NIH3T3 cells, similar to the oncogenic potential exhibited by other Rho-GEF family members. These studies confirm that CDEP is a member of the Rho-GEF family, and has all the utilities associated therewith.

The Examiner further asserts that other utilities that are disclosed in the specification, such as production of and screening of antibodies, allegedly apply to many unrelated polypeptides and are therefore not "specific" to CDEP. Applicants respectfully submit that CDEP has the utilities of a Rho-GEF family member, and the specification discusses these utilities in detail as explained above. These utilities are "specific" to CDEP in that non-Rho-GEF proteins would not have such utilities.

The Examiner acknowledges that the additional asserted utilities such as therapy of osteoarthritis and rheumatoid arthritis, and screening regulators of cell differentiation, are predicted utilities based on homologies to ezrin, Dbl and pleckstrin. However, the Examiner questions whether CDEP would have the same functions as these homologous proteins because homology is not 100%, and sequence dissimilarities upon protein structure and function allegedly cannot be predicted. This aspect of the rejection is supported by several references which purportedly show the sensitivity of proteins to single amino acid substitutions, and which stress the pitfalls of comparative sequence analysis.

Applicants respectfully submit that it is perfectly acceptable to predict a specific utility based on membership in a well-known family of conserved proteins, as the

comments accompanying the Utility Guidelines specifically state. For instance, according to the comments and answers recently published in the Federal Register with the new utility examination guidelines (FR, Vol. 66, No. 4, January 5, 2001), it is perfectly acceptable to assert a specific, substantial and credible utility on the basis of "homology to existing nucleic acids or proteins having an accepted utility." Furthermore, according to this notice, a rigorous correlation is not necessary, only a "reasonable" correlation (see the FR notice, page 1096, middle column continuing into the right hand column). As stated therein, "When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein." Id. In fact, according to the new utility guidelines, "the asserted utility *must* be accepted by the examiner unless the Office has sufficient or sound reasoning to rebut such an assertion." Id. (with emphasis).

Furthermore, the references cited by the Examiner which discount the utility of protein homology comparisons in predicting protein function are irrelevant because CDEP has been shown to be a member of the Rho-GEF family as predicted in the specification. See Koyano et al. (2001), attached hereto. Moreover, there are just as many references available that stress the predictive power of sequence and structure analysis, thereby showing that the references cited by the Examiner present a very one-sided picture of the art.

For instance, in Sreekumar et al. (Current Opinion in Genetics & Dev., 2001, 11: 247-57, attached hereto), the authors stress that the power of sequence and structure

analysis combined with the wealth of genome sequence data will "enable the identification of many new drug targets and accelerate the process of drug design and the development of therapeutic strategies" (page 255, col. 1). Of course, as those of skill in the art are already aware, Sreekumar cautions that alteration of amino acid sequences of functional domains may hamper functioning, particularly when in a highly conserved region or when involving a non-conservative replacement. But this is why it is important to analyze protein sequence information on a case-by-case basis in the context of available experimental data (page 247, col. 2, last paragraph). Indeed, applicants have not predicted the Rho-GEF activity of CDEP based on sequence data alone, but also in view of the experimental data reported in the specification, i.e., that CDEP expression is associated with cellular differentiation and changes in morphology, as might be expected for a Rho-GEF protein serving as a regulatory factor for cytoskeleton binding. See page 34, lines 5-21.

Other references also stress the value of sequence homologies in predicting protein structure and function. For instance, according to an article by Liisa Holm (Current Opinion in Struct. Biol. (1998) 8:372-79, attached hereto), homology is "a most useful concept in computational biology. By inferring homology between two proteins on the basis of sequence similarity, biologists can confidently predict that protein structure and function have also remained similar in evolution" (page 372, col. 1). According to Holm, a "widely used empirical calibration suggested a threshold of 25-30% sequence identity, above which sequence similarity implies structural (and functional) similarity" (page 372, col. 2). The homologies between the relevant protein

domains of CDEP and the other Rho-GEF family members as disclosed in the specification are generally at or above this threshold.

Similarly, D'Alfonso et al. (J. Struct. Biol. (2001) 134: 246-256, attached hereto) also stress the utility of identifying and using sequence homologies as a tool for modeling protein structure. According to D'Alfonso et al., "[c]omparative modeling is based on the observation that sequence similarity above a certain threshold implies structural similarity" (page 246, col. 2). Like Holm, D'Alfonso and colleagues stressed the threshold of 25% sequence identity as one which could be used to analyze "clearly homologous proteins" (page 247, col. 2).

Thus, those of skill in the art clearly recognize the value of sequence homologies for making predictions regarding protein function, as does the U.S. Patent & Trademark Office as reflected in the new Utility Guidelines as discussed above. Not only are the homologies identified in the specification within the acceptable range of utility for making predictions regarding protein function, but applicants have since shown that CDEP possesses the predicted functions. Accordingly, this ground for the utility rejection cannot stand.

The Examiner further argues that the claimed nucleic acid is not specific for differentiated chondrocytes because it is detected in other tissues, and that the disclosed probes are not specific for SEQ ID NO: 1 because two bands were detected in northern blotting analyses using a CDEP-specific probe. The Examiner is correct to observe that CDEP is expressed in cells other than chondrocytes, which suggests a wider utility for the disclosed gene and fragments thereof. For instance, applicants believe that the disclosed

fragments may be used in studying cellular differentiation in many cell types, not only in chondrocytes.

The Examiner is also correct to note that two bands were detected in northern analysis using a CDEP-specific probe. But this does not mean that the disclosed probes are not specific for CDEP. Many genes are known to express transcripts of multiple lengths, so it is not impossible that the second band is also derived from the CDEP gene locus. In any case, applicants have disclosed the sequence of the CDEP gene, so those of skill in the art could readily determine whether sequences homologous or identical to SEQ ID NO: 1 have been identified using well known techniques in the art.

Finally, according to the Examiner's reasoning, even if CDEP expression was specific for differentiated chondrocytes, this still would not satisfy the new utility standards because other nucleic acids are specific for differentiated chondrocytes. Therefore, the asserted utility would still not be "specific" to CDEP. Applicants respectfully submit that CDEP is not specifically expressed in differentiated chondrocytes, as noted above. But even if it were, this would be an unduly harsh standard for evaluating utility.

To make an analogy, if the U.S. Patent & Trademark Office refused to recognize the utility of a new drug just because a prior existing drug was used to treat the same disease, patents could not be obtained for new drugs. Furthermore, patients would be given no new options other than the first drug patented for any particular purpose. By arguing that there are other nucleic acids specific for differentiated chondrocytes so as to destroy a "specific" utility for CDEP in this regard (without, by the way, presenting any

evidence of such other nucleic acids), the Examiner is in effect arguing that novel compounds cannot be patented by virtue of their use in known methods because such methods are not "specific" to the novel compound, even when such methods are specific for a class of compounds and not just any protein in general. Such a standard is untenably stringent and is unsupported by any legal basis.

Furthermore, CDEP need not be specific for differentiated chondrocytes for it to have utility in identifying the same. Applicants have shown that CDEP is expressed in differentiated chondrocytes but not in dedifferentiated chondrocytes, which is the only distinction that need be shown for probes designed from CDEP to have utility in chondrocyte-specific differentiation assays. The fact that it is expressed in other cells may mean that it will find a similar utility in the study of other tissues.

In view of all the remarks submitted above, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §101.

Claims 16, 17, 27-28 and 32 were rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification. Essentially, the Examiner's position is that the claims cover a genus of DNAs that includes variants and fragments, but that variants were not disclosed in the specification, and no common structural attributes or functional attributes were defined. While the Examiner does note that the specification discloses a protein with 85% homology to the relevant domains of SEQ ID NO: 2, the specification and claims allegedly fail to place any limit on which amino acids are subject to substitution or the type of substitution. The Examiner further notes that there are no structural features defined that could be used to

distinguish the claimed variants from the nucleotide sequences in the art. Applicants respectfully traverse the rejection.

First of all, claims 27-28 are directed to nucleic acids and fragments thereof that encode at least ninety amino acids that are complementary to the sequences disclosed in the specification. According to the well-known definition of "complementary," this would encompass sequences having a precise sequence defined as either the complement of SEQ ID NO: 1 (as recited in claim 27), or that are complementary to at least 180 base pairs of SEQ ID NO: 2. Such sequences and fragments are clearly supported by the specification. If the Examiner believes that sequences having 180 base pairs of SEQ ID NO: 2 could not be distinguished from other sequences known in the art, then an art rejection should be set forth showing applicants where such confusing sequences are previously disclosed.

Claim 17 has been amended to clarify that stringent hybridization conditions allow hybridization of nucleic acids having 80% or more homology to a nucleotide sequence ranging from the 49th to 3,183rd bases in SEQ ID NO: 1, which would include a defined genus of nucleic acids that is clearly distinguishable by those of skill in the art. Moreover, claim 17 also requires that such a nucleic acid encode a protein specifically expressed in differentiated chondrocytes versus dedifferentiated chondrocytes, which is clearly a functional attribute that assists to apprise one reading the claim of the scope of the invention.

Likewise, claim 16 also requires that the encompassed nucleic acids be specifically expressed in differentiated chondrocytes versus dedifferentiated

chondrocytes. Moreover, claim 16 goes one step further in defining which domains are subject to high homology (85%) limitations, i.e., the domains recited in components (a), (b) and (c), corresponding to an ezrin-like domain, a DH domain and a PH domain, respectively. The specification also provides a discussion of conservative substitutions in protein variants at page 14, lines 12-18. Therefore, in contrast to what is alleged in the Office Action, the specification and the claims do set forth common structural attributes of the claimed nucleic acids, and the specification does provide guidance as to which portions of the nucleic acids may contain substitutions and which substitutions would be most tolerated.

Claim 32 is dependent on all other claims, and therefore incorporates all the limitations thereof in each context. Thus, it is applicants' belief that the claims as amended are fully supported by the specification, and that one of skill in the art upon reading such claims would be quite able to distinguish nucleic acids falling within the scope of the claims from those which do not. Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph for lack of written description, is respectfully requested.

Claims 14-17, 25-28 and 32 were rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way so as to enable one skilled in the art to make and use the invention. Specifically, the Examiner asserts that because the invention is not supported by a specific and credible asserted utility or a well established utility, one of skill in the art would not know how to use the claimed invention. Applicants respectfully traverse the rejection.

Applicants respectfully submit that the arguments provided above in response to the rejection under 35 U.S.C. §101 should be sufficient to establish that the invention does have at least one, if not several, specific and credible utilities. Indeed, applicants disclosed in the specification (and later proved) that CDEP is a member of the Rho-GEF family of proteins. As such, CDEP would have all the utilities associated with being a Rho-GEF family member, particularly those associated with its involvement in the proliferation and differentiation of cells (see page 12, lines 16-19 of the specification). In any case, even if CDEP was not characterized as a Rho-GEF family member, applicants have shown that CDEP is expressed in differentiated chondrocytes but not in dedifferentiated chondrocytes. This distinction provides the basis for an assay for distinguishing differentiated and non-differentiated chondrocytes, which is clearly supported by the disclosure and could be readily performed by those of skill in the art using the methods disclosed therein. Accordingly, those of skill in the art would know how to use the DNA's and kits claimed in the invention. Reconsideration and withdrawal of this rejection under the enablement paragraph of §112, first paragraph, is respectfully requested.

Claim 16 was individually rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to enable the full scope of the invention. Although the Examiner concedes that the specification is enabling for SEQ ID NO: 1, the Examiner does not believe that the specification teaches how to make and use variants of SEQ ID NO: 2 which are capable of functioning as that which is disclosed. The Examiner refers in particular to the lack of predictability in making amino acid substitutions, and the

alleged lack of a disclosed method for making the claimed variants. Applicants respectfully traverse the rejection.

At pages 13-14 of the specification, applicants disclose that any known method may be used for replacing, deleting or inserting particular amino acid residues, including ordinary genetic engineering methods as disclosed in Sambrook et al. (1989), which is a well known genetic engineering manual. A preferred method is provided by Hill's "The Proteins," which was published in 1979 (see page 14, lines 5-15). Further, applicants provide a list of conservative amino acid substitutions that are most frequently tolerated in proteins, and also define the domains most important for the function of CDEP. And, as described on page 14 (lines 3-5), those of skill in the art could easily select appropriate mutant proteins having functions comparable to CDEP.

For instance, CDEP was disclosed as being a member of the Rho-GEF family of proteins, which are guanine nucleotide exchange factors. According to the attached article by Koyano et al., assays for measuring GDP dissociation from RhoA were available since at least 1994, when Cox and Der disclosed an *in vitro* nitrocellulose binding assay for detecting such activity (cited reference 12). Thus, those of skill in the art could readily prepare mutant CDEP proteins using techniques that have been known in the art since 1979, and could readily screen such mutants for Rho-GEF activity using assays known in the art since at least 1994. Applicants need not disclose what is known in the art to enable those of skill in the art to make and use the invention. Reconsideration and withdrawal of the rejection of claim 16 under the enablement paragraph of §112, first paragraph, is respectfully requested.

claim for variant of unknown function - i.e. claim not limited to Rho-GEF activity

Claims 17, 27-28 and 32 were separately rejected under 35 U.S.C. §112, first paragraph, because of the term "hybridization." According to the Office Action, these claims encompass a variety of species, and a substantial number of "hybridizing" polynucleotides would not share either structural or functional properties with nucleotides 49-3183 of SEQ ID NO: 1 or fragments thereof. Applicants respectfully traverse this ground for rejection.

Again, as applicants noted above with respect to the written description rejection, claims 27 and 28 do not read on hybridizing sequences but on "complementary" sequences. Therefore, these claims do not encompass any nucleotide sequence having a variation from the claimed complementary sequence.

Claim 17, on the other hand, does encompass nucleic acids that hybridize to nucleotides 49-3183 of SEQ ID NO: 1 under stringent conditions, defined as those allowing hybridization of sequences having 80% or more homology. But in addition, claim 17 requires that such sequences are specifically expressed in differentiated chondrocytes as compared to dedifferentiated chondrocytes. This limitation would significantly narrow the number of species encompassed by the claim, and one of skill in the art could readily identify which nucleic acids are included in such a scope and which are not.

Since claim 32 is rejected to the extent that it depends on claims 17, 27 and 28, and these claims are clearly enabled for the reasons provided above, reconsideration and withdrawal of this ground for the rejection under §112, first paragraph, is respectfully requested.

Claims 14-17, 26, 28 and 32 were separately rejected under 35 U.S.C. §112, first paragraph, as to detection of variant proteins falling within the scope of the claims. According to the Office Action, one cannot extrapolate the teachings of the specification to the claims because it is allegedly unpredictable that CDEP will be expressed in tissues in nature. In particular, the Examiner believes that detection in a lung fibroblast line does not mean that CDEP is expressed in tissues *in vivo*, because cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived. Further, the Examiner argues that expression of mRNA does not necessarily mean that the mRNA is translated into protein, and that the claimed protein has not been isolated or detected. Applicants respectfully traverse.

First, Example 4 of the specification describes the use of anti-CDEP antiserum to examine the intracellular location of the CDEP protein. Therefore, the CDEP protein has been detected, and the Examiner's last point is clearly incorrect.

Second, the suggestion that the specification only discloses CDEP expression in a lung fibroblast cell line entirely ignores the fact that the CDEP gene was isolated from chondrocytes isolated from fetal cartilage (see page 24, lines 2-6). It also ignores the showing of CDEP expression in various human fetal tissues in Figures 2A and 2B. For instance, according to Figure 2A, CDEP expression was detected at the highest levels in fetal brain and spleen tissues. According to Figure 2B, expression was intermediate in the kidneys, testis and lung (see page 27, lines 4-15).

Third, functional variants of the disclosed CDEP protein may be isolated using well known techniques that have long been known in the art as discussed above.

Therefore, the argument that detection of CDEP protein or DNA is not enabled because expression in tissues in nature is unpredictable simply ignores the data presented in the specification. Such data may be readily extrapolated to any variant protein encompassed by the claims. Reconsideration and withdrawal of this ground for rejection under §112, first paragraph, is respectfully requested.

Claim 32 was separately rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to enable identification of any differentiated cell. However, the Examiner concedes that the specification enables a kit providing for the identification of a differentiated chondrocyte from a dedifferentiated chondrocyte. While applicants believe that the presence of CDEP in various human fetal tissues and its role as a Rho-GEF protein warrant the prediction that it may play a role in the differentiation of cell types other than chondrocytes, applicants have amended claim 32 such that it is limited to distinguishing differentiated chondrocytes in order to expedite prosecution. Reconsideration and withdrawal of this ground for rejection under §112, first paragraph, is respectfully requested.

Claims 17, 25 and 27 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Koyano et al., 1997, BBRC, 241(2): 369-75, and by GenBank accession number AB008430, allegedly publicly available in 1997. Both of the references allegedly disclose a sequence with 100% similarity to SEQ ID NO: 1. Applicants respectfully traverse the rejections.

First, the cited BBRC article was published on December 18, 1997, as shown by the attached PubMed abstract. Therefore, this article is not prior art to the present application, which is entitled to a foreign priority date of October 28, 1997.

Second, although the GenBank listing indicates that the date of submission of the CDEP sequence was October 22, 1997, this does not mean that the sequence was publicly available on that date as alleged in the Office Action. Indeed, as explained in the GenBank Overview information, a copy of which is attached hereto, many journals require submission of sequence information prior to publication so that an accession number may appear in the paper. However, GenBank will retain the information as confidential for a designated period of time, or until a reference disclosing the sequence is published. In fact, according to GenBank, one should send a message to info@ncbi.nlm.nih.gov to request the date of first public release for any sequence entry, as it is not provided in the listing.

We contacted GenBank to verify the date of public release of accession number AB008430, who in turn placed us in contact with the DNA Data Bank of Japan (DDBJ). According to an email we received from a representative at DDBJ in response to our inquiry (email attached hereto), the sequence with accession number AB008430 was released from DDBJ on January 10, 1998. Therefore, the GenBank accession number is not prior art to the present application, which is entitled to a foreign priority date of October 28, 1997. Reconsideration and withdrawal of the rejections under §102(b) based on the BBRC reference and the GenBank listing are respectfully requested.

Claim 32 was rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Koyano et al. (BBRC). Although Koyano does not disclose a kit comprising a nucleic acid sequence, the Examiner believes such a kit would be an obvious extension of the teachings of Koyano et al., which teach the SEQ ID NO: 1. The use of the disclosed nucleic acid in a kit is alleged to be obvious because "it is common in the art to make and use a kit comprising a compound for commercial purposes." Applicants respectfully traverse the rejection.

Applicants disagree with the examiner's reasoning because it would not be obvious to make and use a kit based solely on the disclosure of the sequence itself. In order to make and use a kit for commercial "purposes," one would need to know the purpose for which the kit is designed. Nevertheless, seeing as the BBRC article was published in December, 1997, it is not prior art against the present invention, which is entitled to a priority date of October 28, 1997. Therefore, withdrawal of the rejection of claim 32 under 35 U.S.C. §103(a) is respectfully requested.

This Reply is fully responsive to the Office Action dated December 19, 2001. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, he[she] is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted
Morgan, Lewis & Bockius LLP

Dated: March 19, 2002

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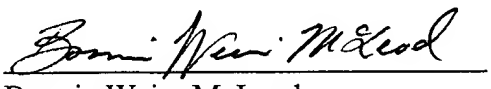
By: 
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APPENDIX

The following amendments were made to the specification and claims:

IN THE SPECIFICATION:

At the paragraph bridging pages 5-6:

--Fig. 1 is a view showing a nucleic acid nucleotide sequence of CDEP cDNA (SEQ ID NO: 1), and an amino acid sequence deduced therefrom (SEQ ID NO: 2), in which ezrin-like domain is indicated by an open frame, DBL homology (DH) domain is underlined, pleckstrin homology (PH) domain is double-underlined, an asterisk downstream from a protein coding region represents a stop codon, a poly(A) addition signal is indicated by a dashed line, and a poly(A) addition site is indicated by a triangle;--.

At the paragraph bridging pages 6-7:

--Figure 3 is a view showing the arrangement of an ezrin-like domain and a Dbl homology (DH) domain, and comparisons among ezrin-like domains of human CDEP (SEQ ID NO: 23), ezrin (SEQ ID NO: 24), and band 4.1 (SEQ ID NO: 25), in which the residues conserved with respect to CDEP are indicated in bold type;--.

At the paragraph at page 7, lines 2-5:

--Fig. 4 is a view showing comparisons among DH domain of human CDEP (SEQ ID NO: 26), human Dbl (SEQ ID NO: 27), rat Ost (SEQ ID NO: 28), mouse [Est2] Ect2

(SEQ ID NO: 29), and human FGD1 (SEQ ID NO: 30), in which the residues conserved with respect to CDEP are indicated in bold type;--.

At the paragraph at page 29, lines 12-21:

--Total RNA was extracted from each of layers, i.e, costal cartilage growth plate slices (a portion near the bone side was divided into three parts designated as G3, G2 and G1) and a resting cartilage layer (called R) of a 4-weeks-old male Japanese albino rabbit. The extract was examined for the expression level of CDEP mRNA by the RT-PCR method. The expression levels of type X collagen, alkaline phosphatase, and proteoglycan [aggrecan], differentiation markers of chondrocytes, in the respective layers were confirmed by RT-PCR.--

IN THE CLAIMS:

Claim 14 was canceled.

15. (Amended) An isolated DNA encoding [the] a protein [according to claim 12] having an amino acid sequence as set forth in SEQ ID NO: 2.

16. (Amended) An isolated DNA encoding [the] a protein [according to claim 13] comprising an amino acid sequence set forth in SEQ ID NO: 2 in which one to several amino acids have been deleted, substituted or added, the protein being specifically

expressed in differentiated chondrocytes versus dedifferentiated chondrocytes, and the protein being such that

(1) the amino acid sequence of a portion of the protein corresponding to an amino acid sequence ranging from the 1st to 374th amino acids in SEQ ID NO: 2 in the sequence listing has homology of 85% or more to the amino acid sequence ranging from the 1st to 374th amino acids in the SEQ ID NO: 2,

(2) the amino acid sequence of a portion of the protein corresponding to an amino acid sequence ranging from the 544th to 737th amino acids in SEQ ID NO: 2 in the sequence listing has homology of 85% or more to the amino acid sequence ranging from the 544th to 737th amino acids in the SEQ ID NO: 2, and

(3) the amino acid sequence of a portion of the protein corresponding to an amino acid sequence ranging from the 764th to 854th amino acids in SEQ ID NO: 2 in the sequence listing has homology of 85% or more to the amino acid sequence ranging from the 764th to 854th amino acids in the SEQ ID NO: 2.

17. (Amended) [A] An isolated gene comprising DNA shown in the following (a) or (b):

(c) DNA having a nucleotide sequence ranging from the 49th to 3,183rd bases in a nucleotide sequence set forth in SEQ ID NO: 1 [in the sequence listing]; and

(d) DNA which is hybridized under stringent conditions with DNA having a nucleotide sequence ranging from the 49th to 3,183rd bases in a nucleotide

sequence set forth in SEQ ID NO: 1 [in the sequence listing], and which encodes a protein specifically expressed in differentiated chondrocytes as compared to dedifferentiated chondrocytes, wherein stringent conditions are defined as those which permit hybridization of DNA's having a homology of 80% or more to SEQ ID NO: 1, but at which nucleic acids having lower homology do not hybridize.

32. (Amended) A kit for [identifying] distinguishing a differentiated [cell] chondrocyte from a dedifferentiated chondrocyte comprising at least one of the [following components:

(a) any one of the] nucleic acids of claims [14]15-17[,] and 25-28[29;

(b) any one of the proteins of claims 11-13; or

(c) an antibody according to claims 19-21].